

Associations of informant-based sleep reports with Alzheimer's disease pathologies

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Purpose: Recent studies have found associations of increased brain amyloid beta ($A\beta$) accumulation and several abnormal sleep-wake patterns, including shorter latency and increased fragmentation in preclinical Alzheimer's disease (AD). There is little known about the relationship between sleep and tau. The objective of this study was to understand the associations of both tau and $A\beta$ with early signs of sleep and night-time behavior changes in clinically normal elderly adults. Specifically, we have addressed the question of how informant-based subjective sleep reports are linked to regional [^{18}F]florbetapir and [^{18}F]florbetapir uptake.

Methods: Imaging and behavioral data from 35 subjects were obtained from the Alzheimer's Disease Neuroimaging Initiative. The Neuropsychiatric Inventory Sleep (NPI-sleep) Questionnaire was used to assess the sleep and night-time behavior changes. Regional tau-positron emission tomography (PET) (entorhinal, brainstem) and $A\beta$ -PET (posterior cingulate, precuneus, medial orbitofrontal) uptake values were calculated. A series of linear regression analyses were used to determine the combination of sleep symptoms that built the best models to predict each pathology.

Results: Informant-based reports of abnormal night-time behavior (NPI questions k3, k5, and k8) were significantly associated with increased entorhinal tau and $A\beta$ (all regions) accumulation. Interestingly, informant-based reports of sleep deficiencies without abnormal night-time activity (NPI questions k1, k2, and k6) were negatively associated with entorhinal tau burden.

Conclusion: Detection of abnormal night-time behaviors (wandering, pacing, other inappropriate activities) by family members indicates early signs of both AD pathologies and may encourage the affected individuals to seek help by health care providers for detailed cognitive/neurobehavioral assessments.

Keywords: $A\beta$, tau, positron emission tomography, mild cognitive impairment, sleep, neuropsychiatric inventory

Introduction

Sleep and circadian rhythm disturbances are frequent in Alzheimer's disease (AD)¹⁻⁵ and may appear before the onset of the clinical symptoms. Abnormal sleep patterns can be detected and quantitatively characterized by traditional polysomnography and motion-based actigraphy devices. An increasing number of actigraphy studies have reported associations between increased brain amyloid beta ($A\beta$) burden and several abnormal sleep-wake patterns, including shorter sleep latency⁶ and increased night-time sleep fragmentation⁷ as early as in clinically normal elderly adults. Self-reported and informant-based questionnaires can also help evaluate the overall sleep quality. While these subjective assessments do not

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provide accurate measures of sleep-wake patterns, they can be administered without the necessity of recording sleep data for a period of time. Spira et al found associations of self-reported measures of excessive daytime sleepiness/napping with elevated A β burden in cognitively normal community-dwelling elderly adults.⁸ Another study on non-demented late-middle-aged adults found that participants with self-reported sleep problems and inadequate sleep had greater amyloid burden in several AD-sensitive regions, including medial orbitofrontal cortex, cingulate gyrus, and precuneus.⁹ In comparison to A β , there is little known about the relationship between sleep and tau. The influence of tau pathology could be relevant to the sleep-wake alterations in AD, possibly due to the presence of abnormal tau accumulation in sleep-regulating regions such as brainstem.^{10,11}

The objective of this study was to understand the associations of both A β and tau with early signs of changes in sleep and night-time behavior in clinically normal elderly adults. Specifically, we have addressed the question of how informant-based subjective sleep reports are linked to regional [¹⁸F]florbetapir and [¹⁸F]florbetapir uptake. Sleep disturbances are among the major causes of patient institutionalization in AD.¹² Simple sleep questionnaires that can be readily administered and evaluated by family members may play an important role in detecting early warning signs of AD and encourage the affected individuals to seek help by health care providers for cognitive/neurobehavioral assessments. Detailed characterization of subjective reports of sleep and night-time behavioral changes may render a valuable pre-screening tool for pathological prediction.

Materials and methods

Study populations

Data were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). This study was approved by the Institutional Review Board of Vanderbilt University Medical Center (#181429). ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early AD. Demographic, clinical,

and imaging data for this study were collected from 35 clinically normal ADNI subjects who had A β PET scan, tau PET scan, and at least one abnormal sleep change in their informant-based sleep report. ADNI CN subjects have a Mini-Mental State Examination, MMSE¹³ memory scores of 24–30 (inclusive), a clinical dementia rating of 0, and education-adjusted score on delayed recall of paragraph A from Wechsler Memory Scale Logical Memory II (E-WMS) ≥ 9 for 16 or higher educational years, ≥ 5 for 8–15 years of education, ≥ 3 for 0–7 years of education. CN subjects are not diagnosed with dementia or MCI.

The Neuropsychiatric Inventory Sleep Questionnaire (NPI-sleep)

NPI is based on questions addressed to an informed caregiver to assess behavioral changes including sleep problems. The NPI-sleep questionnaire pertains to recent changes in the patient's sleep behavior. The initial question determines the presence or absence of abnormal sleep changes. A positive answer (presence of resent sleep problems) is followed by eight questions (k1–k8) to determine the specific nature of the abnormal sleep behavior. These include difficulties in falling asleep (k1), getting up during the night (k2), pacing and wandering at night (k3), awakening the caregiver during night (k4), awoken at night or too early in the morning and thinking that it is time to start the day (k5), waking up too early in the morning (k6), excessive daytime napping (k7), and other abnormal night-time behaviors (k8). The NPI-sleep questionnaire is summarized in Table 1.

PET data acquisition and preprocessing

All ADNI [¹⁸F]Florbetapir (for A β) and [¹⁸F]Flortaucipir (for tau) scans were acquired at participating sites and

Table 1 NPI-sleep questions

Index	Question
K1	Does participant have difficulty falling asleep?
K2	Does participant get up during night?
K3	Does participant wander, or get involved in inappropriate activities at night?
K4	Does participant awaken you during night?
K5	Does participant awaken at night, and plans to start the day?
K6	Does participant awaken too early in the morning?
K7	Does participant sleep excessively during the day?
K8	Does participant have other bothering night-time behaviors?

followed the standardized ADNI PET protocols (adni.loni.usc.edu).

Tau PET

The PET acquisitions started with the injection of 370 MBq $\pm 10\%$ of [^{18}F]Flortaucipir and followed by a 30 mins (6×5 mins frames) scan starting at 75–105 mins after the injection. All ADNI [^{18}F]Flortaucipir images were uploaded to University of Southern California Laboratory of Neuroimaging (LONI) where they were preprocessed and the regional tracer uptakes were calculated in LONI by using Freesurfer-defined cortical regions on the subjects' T1-weighted volumetric MP-RAGE. The Freesurfer processing of MRI volumes included skull-stripping, segmentation, and delineation of cortical and subcortical regions. Subjects' PET frames were coregistered, averaged, and smoothed to obtain a resolution of 8 mm full width at half maximum. The regional gray matter masks were applied to PET images to extract the mean uptake values, which were divided by the cerebellar gray matter uptake to determine the standardized uptake value ratios (SUVRs). The size of these regions and their mean PET uptake values are available for download in ADNI archive. The mean regional tau PET uptake values from three regions (left and right entorhinal and brainstem) were downloaded. The entorhinal cortex was selected because it is one of the earliest affected regions by tau pathology.¹⁴ Brainstem was selected due to its importance as a sleep-regulating region.^{10,11}

A β PET

The PET acquisitions started with the injection of 370 MBq $\pm 10\%$ of [^{18}F]Florbetapir and followed by a 20 mins scan starting 50 mins post-injection.¹⁵ Similar to ADNI tau acquisition and processing, all [^{18}F]Florbetapir images were uploaded to the LONI where they were preprocessed and the regional masks were calculated by using Freesurfer-defined cortical regions on the subjects' T1-weighted MRI volumes. We downloaded the mean regional A β PET uptake values from six regions (left and right posterior cingulate, left and right precuneus, left and right medial orbitofrontal) and normalized them by the whole cerebellum. These regions were selected because they are known to be affected early by the A β accumulation.^{16–18} In addition to regional A β uptake values, the mean A β tracer uptake from a cortical summary region of interest (ROI) was downloaded to determine whether a subject is A β -positive or A β -negative. The

summary ROI consisted of four cortical regions (frontal, anterior/posterior cingulate, lateral parietal, lateral temporal). The weighted means of these regions were calculated and divided by the whole cerebellum mean uptake. A threshold of 1.11 was applied to determine the A β status.

Statistical analysis

Each NPI-sleep question (k1–k8) was scored by the informant (zero for the absence and one for the presence of each specific symptom). To determine associations between each regional A β /tau accumulation and informant-based sleep reports, we conducted three steps of regression analysis starting with a backward-elimination regression¹⁹ for each pathology (regional tau and A β SUVR values) as outcome. The sleep symptoms k1–k8 were included as categorical variables. The backward-elimination process tests the removal of each predictor using a chosen model fit criterion (Akaike information), and step-wise removing predictors with the most statistically insignificant deterioration of the fit to determine which combination of variables (from k1–k8) builds the strongest model to fit a given pathological measure. The sleep variables of the strongest model were subsequently included in a second linear regression model as predictors along with age, sex, and Apolipoprotein E4 (APOE- $\epsilon 4$) status as covariates to determine the sign of the coefficients associated with each sleep variable for predicting each regional A β /tau accumulation (outcomes). A positive coefficient sign indicates that as the predictor increases, the outcome variable also increases. A negative sign indicates that as the predictor increases, the outcome variable decreases. For each regional A β /tau, the scores of all sleep variables with the same direction (positive or negative) of coefficient sign were added together and included as non-categorical variable (total score) in a third linear regression model to determine how these total scores predicted the corresponding regional A β /tau burden. [Figure 1](#) illustrates the described statistical analyses pipeline for a single regional SUVR (example: A β SUVR in the posterior cingulate cortex).

Results

Data from 35 CN subjects were used for this study ([Table 2](#)). Approximately, half of the subjects were APOE- $\epsilon 4$ carriers and had A β -positive scans. Sixty-six percent of the subjects were women.

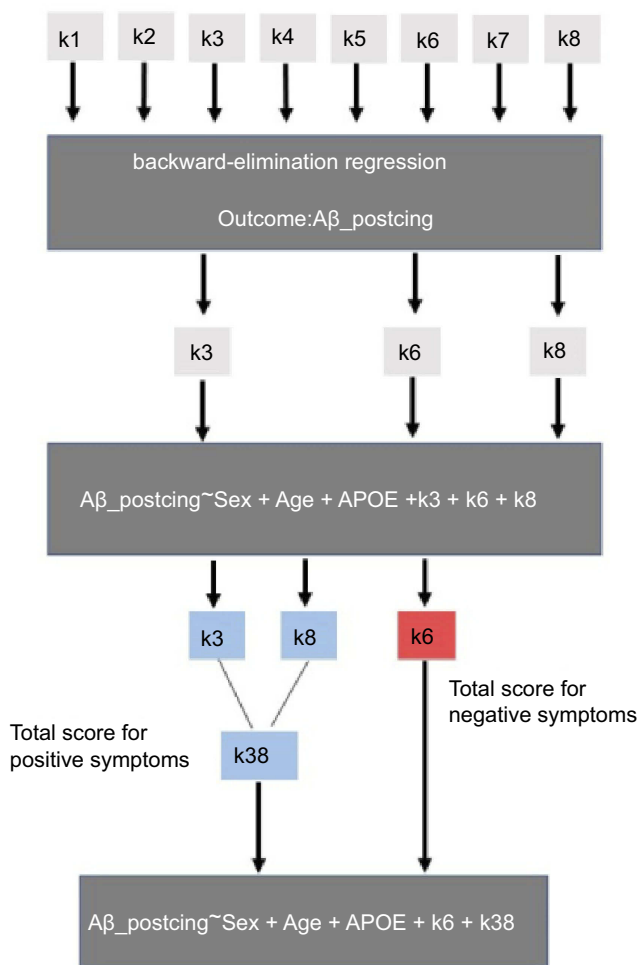


Figure 1 Pipeline of the statistical analyses.

Table 2 Subject characteristics

Variable	Value
Number of subjects	35
Number of women	23
Age, years (mean±SD)	77±7
APOE-ε4 carriers (%)	28%
Global Aβ levels (SUVR)	1.14±0.18
Aβ-positive (%)	30%

Abbreviations: APOE-ε4, apolipoprotein ε4; SUVR, standardized uptake value ratio.

Backward-elimination regression analysis

Table 3 shows the NPI-sleep questionnaires that were selected by the backward-elimination regression process as the combination of predictors building the strongest model for predicting each regional Aβ burden (rows). The non-empty cells indicate the presence of the NPI symptom (with either positive or negative correlation) in

the strongest backward elimination model. For most Aβ regions, the NPI-sleep scores k3 (abnormal wandering and pacing at night), k6 (awaken earlier than was his/her habit), and k8 (other abnormal night-time behavior) were present in the strongest models for predicting Aβ burden. The coefficient signs were positive for k3 and k8 but negative for k6. Excessive sleep during day (k7) was not present in any of the strongest models.

Table 4 shows the NPI-sleep questionnaires that were selected by the backward-elimination regression process as the combination of predictors (both positive and negative) building the strongest model for predicting each regional tau burden (rows). In the entorhinal cortex, k1, k2, and k6 were associated with negative coefficients whereas k3, k4, k5, and k8 were associated with positive coefficients. The best model for brainstem did not include any of the eight symptoms. Excessive sleep during day (k7) was not present in any of the strongest models.

Regression analyses with total scores

Table 5 presents the regression analyses with the total scores (regional SUVR~Age+Sex+APOE+total_score_pos+total_score_neg). For regional Aβ SUVR values, k3 and k8 appeared in the strongest models and had positive coefficients. Therefore, the total score of symptoms with positive coefficients (total_score_pos) was calculated as the sum of their scores (k38). The questionnaire k6 was the only symptom that appeared in the strongest model and was associated with a negative coefficient. For the left entorhinal SUVR value, the sleep symptoms k3, k5, and k8 appeared in the strongest models and had positive coefficients. Therefore, the total score of symptoms with positive coefficients for this region was calculated as the sum of scores from k3, k5, and k8 questions (k358). For the right entorhinal SUVR value, the sleep symptoms k3, k4, and k8 appeared in the strongest models and had positive coefficients. Therefore, the total score of symptoms with positive coefficients for this region was calculated as the sum of scores from k3, k4, and k8 (k348). The symptoms k1, k2, and k6 were associated with negative coefficients for both left and right entorhinal SUVR values. Therefore, the total score of symptoms with negative coefficients (total_score_neg) for these two regions was calculated as the sum of scores from k1, k2, and k6 questions (k126). Brainstem was left out because none of the symptoms appeared in the strongest model for this region. Age, sex, and APOE were added as other covariates. The Bonferroni-corrected P-value of 0.006 was used to adjust for multiple

Table 3 NPI-sleep symptoms (columns) in the strongest models for predicting regional A β burden (rows). Non-empty cells indicate the presence of the symptom (positive or negative correlation) in the strongest model determined by the backward-elimination process

Region	k1	k2	k3	k4	k5	k6	k7	k8
L_Post			positive			negative		positive
R_Post			positive			negative		positive
L_Precun			positive			negative		positive
R_Precun			positive			negative		positive
L_Med_orb_front			positive			negative		positive
R_Med_orb_front			positive			negative		

Abbreviations: L_post, left posterior cingulate cortex; R_post, right posterior cingulate; L_precun, left precuneus; R_precun, right precuneus; L_Med_orb_front, left medial orbitofrontal cortex; R_Med_orb_front, right medial orbitofrontal cortex.

Table 4 NPI-sleep symptoms (columns) in the strongest models for predicting regional tau burden (rows). Non-empty cells indicate the presence of the symptom (positive or negative correlation) in the strongest model determined by the backward-elimination process

	k1	k2	k3	k4	k5	k6	k7	k8
L_Entorhinal	negative	negative	positive		positive	negative		positive
R_Entorhinal	negative	negative	positive	positive		negative		positive
Brainstem								

comparisons across regional A β and tau measures (left and right posterior cingulate, left and right precuneus, left and right medial orbitofrontal, left and right entorhinal). We found that the total score of symptoms with positive coefficients (k38 for A β , k358 for left entorhinal, k348 for right entorhinal) were significantly associated with elevated tau (both left and right entorhinal) and elevated A β (posterior cingulate and precuneus). For the medial orbitofrontal regions, the P-value was above the Bonferroni-adjusted threshold. The total score of symptoms with negative coefficients (k1, k2, k6) was significantly associated with both left and right entorhinal tau SUVR values. Only the left precuneus SUVR was marginally associated with k6. To show the tracer accumulation in subjects with different sleep symptoms, the subjects were roughly stratified based on the severity of each composite positive/negative sleep score (k38, k6, k358, k126). Group comparisons for global A β and left entorhinal tau are shown in Figure 2. A Student's *t*-test was conducted to determine the group differences. The associated P-values were 0.03 for group differences in global A β -PET SUVR when subjects were stratified based on the positive composite score k38 (k38=0 in group 1 and k38>0 in group 2) and 0.56 when they were grouped based

on the negative score k6. For entorhinal tau, the P-values were 0.047 for group differences when subjects were stratified based on the positive composite score k358 and 0.066 when they were divided based on the negative composite score k126. The subjects' data and the script for statistical analysis can be found in supplementary materials.

Discussion

Current sleep assessment methods can be classified based on different criteria, such as objectivity (polysomnography and actigraphy vs subjective sleep questionnaires) and need for medical assistance (administered by clinician vs self-assessment). The primary goal of this study was to understand the associations between AD pathologies (A β and tau) and simple sleep questionnaires that can be readily administered and interpreted by family members. Given that sleep disturbances are among the major causes of patient institutionalization in AD,¹² detecting earliest abnormal signs of altered sleep patterns may motivate the caregivers and affected individuals to seek help by health care providers who can provide more detailed cognitive/neurobehavioral assessments. The findings of this study indicate the presence of two distinct sleep-related patterns reported by

Table 5 Regression analyses with total scores. For regional A

Aβ_SUVR~Age+Sex+APOE+k38+k6						
Symptom(s) with positive coefficient: k38 (sum of k3 and k8 scores)				Symptom(s) with negative coefficients: k6		
Region	β (95% CI)	R ²	P-value	β (95% CI)	R ²	P-value
L_Post	0.45 (0.36, 0.54)	0.56	<0.0001*	-0.18 (-0.25, -0.10)	0.56	0.026
R_Post	0.47 (0.38, 0.56)	0.58	<0.0001*	-0.20 (-0.28, -0.13)	0.58	0.012
L_Precun	0.50 (0.40, 0.60)	0.57	<0.0001*	-0.23 (-0.31, -0.14)	0.57	0.013
R_Precun	0.53 (0.43, 0.63)	0.60	<0.0001*	-0.26 (-0.34, -0.17)	0.60	0.006
L_Med_orb_front	0.32 (0.21, 0.43)	0.32	0.009	-0.20 (-0.30, -0.11)	0.32	0.04
R_Med_orb_front	0.34 (0.22, 0.46)	0.34	0.008	-0.23 (-0.33, -0.13)	0.34	0.03
tau_SUVR~Age+Sex+APOE+k358+k126						
Symptom(s) with positive coefficient: k358 (sum of k3, k5, and k8 scores)				Symptom(s) with negative coefficients: k126 (sum of k1, k2, and k6 scores)		
Region	β (95% CI)	R ²	P-value	β (95% CI)	R ²	P-value
L_entorhinal	0.21 (0.17, 0.25)	0.68	<0.0001*	-0.15 (-0.19, -0.11)	0.68	0.0004*
tau_SUVR~Age+Sex+APOE+k348+k126						
Symptom(s) with positive coefficient: k358 (sum of k3, k4, and k8 scores)				Symptom(s) with negative coefficients: k126 (sum of k1, k2, and k6 scores)		
Region	β (95% CI)	R ²	P-value	β (95% CI)	R ²	P-value
R_entorhinal	0.22 (0.18, 0.26)	0.71	<0.0001*	-0.20 (-0.24, -0.16)	0.71	<0.0001*

Note: *P<0.005; bold values indicate significance.

Abbreviations: L_post, left posterior cingulate cortex; R_post, right posterior cingulate; L_precun, left precuneus; R_precun, right precuneus; L_Med_orb_front, left medial orbitofrontal cortex; R_Med_orb_front, right medial orbitofrontal cortex.

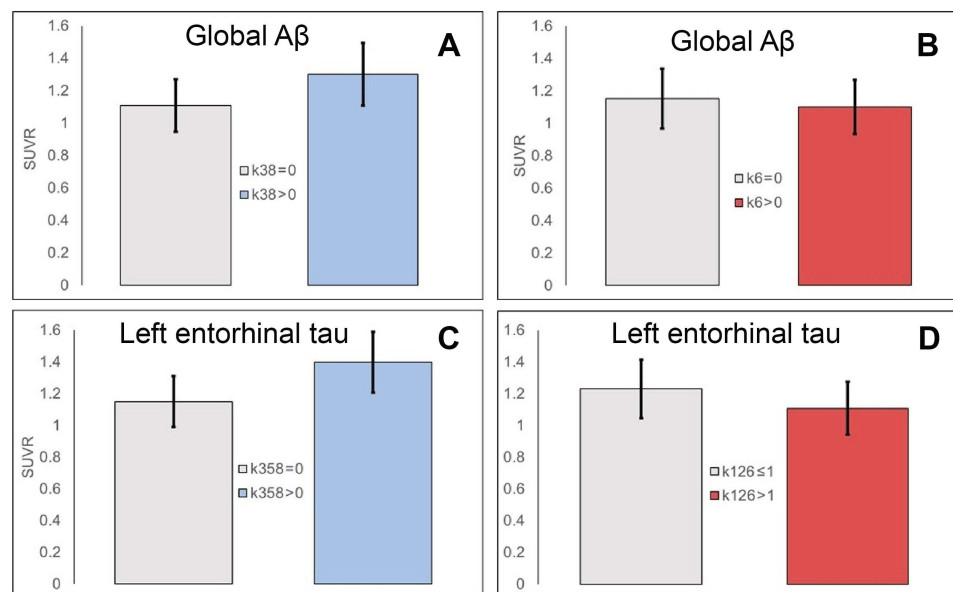


Figure 2 Global A β PET and left entorhinal tau SUVR values in subject groups stratified by the presence/absence of symptoms with positive coefficients (k35 for A β in **A**, k358 for tau in **C**) and negative coefficients (k6 for A β in **B** and k126 for tau in **D**).

informants and their differential associations with AD pathologies. We found that informant-reported symptoms related to abnormal night-time behavior (k3, k4, k5, k8)

were positively associated with both pathologies meaning that the presence of abnormal night-time activities and increased number of night-time behavioral symptoms (k38

for A β , k358 for left entorhinal tau, and k348 for right entorhinal tau) were associated with elevated levels of both A β and tau. Interestingly, we found that informant-reported symptoms related to sleep deficiency, difficulties falling asleep (k1), fragmented sleep (k2), awoken too early (k6), without the involvement of abnormal behavioral activities (wandering, pacing, get ready to go to work), were significantly associated with lower entorhinal tau burden (but no significant associations with A β). Given the previously observed relationships between self-reported sleep deficiencies and elevated A β levels, the lack of such associations with informant-based reports on sleep deficiency may indicate that self-reports are potentially better in detecting sleep deficiencies than informant-based reports. However, the negative associations of sleep deficiencies and entorhinal tau were somehow surprising. While a large number of previous research have established a consistent link between sleep deficiencies and elevated amyloid across human subjects^{7,20,21} and animal models,²² little is known about how sleep deficiencies are linked to the progression of tauopathy. Specifically, previous sleep-tau studies on animals were conducted by evoking acute sleep deprivation on animals with seeded tau in their brains.²³ It remains to be explored how findings of these experimental studies on nocturnal animals (different circadian rhythm than human) can be translated into human subjects where tau deposits are also found in normal aging. Using actigraphy on a population of older cognitively normal adults, Kam et al²⁴ reported no correlations between cerebrospinal fluid measures of total tau (t-tau) and phosphorylated (p-tau) and measures of sleep quality or habitual sleep duration. Another study by Sprecher et al²⁵ found that worse self-reported subjective sleep quality, more sleep problems, and daytime somnolence were associated with greater AD pathology, indicated by higher t-tau/A β 42, p-tau/A β 42. These different findings may be explained by differences in the use of subjective versus objective measures and self-report versus informant-report of sleep used across these studies. One of the limitations of this study is the small sample size. We included only subjects who had both A β and tau scans. Also, due to the nature of the statistical analysis, we could only include subjects who had at least one sleep symptom (one of eight questions).

The progression of A β plaques starts decades before the onset of dementia. Non-demented individuals with abnormal A β levels show impaired cognitive performance, particularly in episodic memory,²⁶ which is detectable but stable during a long preclinical period²⁷ prior to the manifestation of clinical

AD, thus reflecting a relatively slow progression of pathological (eg, A β) processes that affect the episodic memory. It is not fully understood whether sleep disorders precede episodic memory decline. Based on a group of community-dwelling participants, Spira et al⁸ found that sleep disorders in clinically normal subjects increased the odds (by 2.5 times) of developing A β accumulation 15.7 \pm 3.4 years later. Increasing evidence suggests that the glymphatic system, a recently discovered macroscopic waste clearance system, is responsible for removing metabolites and neurotoxic waste products including A β .²⁸ The glymphatic system is mainly active during sleep suggesting that sleep disorders can contribute to A β accumulation by impairing the glymphatic function. It is possible that sleep disorders may precede episodic memory alterations that occur due to A β progression.

One of the limitations of this study is the small sample size. We searched for all clinically normal ADNI subjects who had both A β and tau PET scans and that these scans were acquired at time points close to each other and the sleep assessments. The rigid timing specifications reduced the number of available subjects. Therefore, this study should be investigated in larger research populations using informant-based or subject-based sleep reports to determine how they predict different AD biomarkers. The Neuropsychiatric Inventory Sleep Questionnaire (NPI-sleep) could be both a strength and a weakness in this study. NPI-sleep questions are simple and can be readily administered and understood by non-clinicians. Only a positive answer to the initial NPI-sleep question (presence of resent sleep problems) is followed by the eight remaining questions to characterize the nature of the sleep problem. However, without the specific and detailed questions (k1–k8), some informants may be unaware of the presence of a sleep problem. Pittsburgh Sleep Quality Index²⁹ is a more effective sleep assessment, which consists of 19 individual items and may deem better for characterizing sleep disorders and detecting associations with AD pathologies. The NPI-sleep questionnaire pertains to recent changes in sleep behavior. However, previous studies⁸ suggest that specific alterations in sleep patterns (eg, excessive daytime napping) occur decades before developing A β accumulation. Therefore, NPI-sleep may not be a suitable test for subjects with a long history of sleep problems.

Conclusion

Detection of abnormal night-time behaviors (wandering, pacing, other inappropriate activities) by family members indicates early signs of both A β and tau pathologies and may encourage the affected individuals to seek help by

health care providers for detailed cognitive/neurobehavioral tests.

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Disclosure

The author reports no conflicts of interest in this work.

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Supplementary materials

Sex	APOE	Age	ent_L	Ent_R	K1	K2	K3	K4	K5	K6	K7	K8	K38	pk358	k358	k126	k348	abeta	medfront_L	medfront_R	postcng_L	postcng_R	precum_L	precum_R
1	0	74.4	1.28	1.2	0	0	0	0	1	1	0	0	0	1	1	1	0	1.05	0.99	0.98	1.27	1.21	1.21	1.16
1	NaN	76.9	1.25	1.3	1	0	0	0	0	0	0	0	0	0	0	1	0	1.17	1.17	1.29	1.14	1.08	1.06	1.14
1	NaN	69.4	1.61	1.62	0	1	0	0	0	0	0	0	0	0	0	1	0	1.51	1.55	1.49	1.63	1.56	1.64	1.59
1	0	92.4	1.74	1.6	0	0	1	1	1	1	0	0	1	1	2	1	2	1.42	1.4	1.42	1.64	1.54	1.59	1.58
1	1	81.5	1.15	1.21	0	0	0	0	0	1	0	0	0	0	0	1	0	1.01	0.88	0.9	1.16	1.13	1.08	1.05
1	NaN	65.3	1.24	1.24	0	1	0	0	0	0	0	1	1	1	1	1	1	1.09	0.98	1.04	1.12	1.07	1.08	1.06
1	1	73.7	1.1	1.04	0	1	0	0	0	0	0	0	0	0	1	0	0	1.24	1.01	0.91	1.1	1.13	0.98	0.98
0	0	75.8	1.15	1.21	1	1	0	1	1	1	0	1	1	1	2	3	2	1.09	0.91	0.88	1.32	1.22	1.18	1.06
1	0	87.2	1.28	1.19	0	1	0	0	0	0	1	0	0	0	0	1	0	1.24	1.22	1.27	1.4	1.43	1.34	1.34
0	0	91.4	1.23	1.28	0	1	0	0	0	0	0	0	0	0	0	1	0	1.13	1.18	1.26	1.14	1.18	1.13	1.14
1	0	84	0.97	0.99	0	1	0	1	0	1	0	0	0	0	0	2	1	0.93	0.85	0.9	1.05	1.02	1.13	0.94
1	0	84.5	1.09	1.14	0	1	0	0	0	0	0	0	0	0	0	1	0	1.11	1.13	1.15	1.23	1.27	1.01	1.32
1	NaN	66.3	1.09	1.15	1	0	0	0	0	0	0	0	0	0	0	1	0	1.09	1.07	1.09	1.17	1.18	1.13	1.18
0	0	79	1.05	1.04	0	1	0	0	0	0	0	0	0	0	0	1	0	1	0.97	0.94	1.09	1.11	1.01	1.02
1	0	69.3	1.11	1.19	1	1	0	0	0	0	1	0	0	0	0	2	0	0.99	0.89	0.98	1.06	1.08	0.99	1.03
1	0	77.3	0.94	0.92	1	1	0	0	0	0	0	0	0	0	0	2	0	1.39	1.3	1.36	1.52	1.45	1.57	1.52
0	0	85.4	1.12	1.18	0	1	1	0	0	1	0	0	1	1	1	2	1	1.22	1.18	1.27	1.33	1.46	1.35	1.52
0	1	83.6	1.2	1.13	0	1	0	0	0	0	0	0	0	0	0	1	0	1.14	1.96	0.95	1.31	1.26	1.3	1.18
0	NaN	73.4	1.12	1.14	1	1	0	1	0	0	0	0	0	0	0	2	1	1.17	1.1	1.15	1.34	1.41	1.3	1.37
1	NaN	65.7	1.07	1.01	1	0	0	0	0	0	0	0	0	0	0	1	0	1.06	0.98	0.99	1.16	1.2	1.16	1.16
0	0	82.4	1.14	1.22	0	1	0	0	0	0	0	0	0	0	0	1	0	0.97	0.88	0.86	1.06	1.05	0.96	1.02
0	1	71.3	1.09	1.18	0	1	0	0	0	0	0	0	0	0	0	1	0	1.04	1.05	1.04	1.28	1.29	1.13	1.15
1	1	80.8	1.32	1.35	0	1	0	0	0	0	0	0	0	0	0	1	0	1.14	0.81	0.94	1.25	1.29	1.3	1.28
1	0	74.6	1.13	1.1	0	1	0	0	0	1	0	0	0	0	0	2	0	0.98	1	0.94	1.07	1.07	0.99	1.02
0	0	68.8	1.09	1.12	1	1	0	1	0	0	0	0	0	0	0	2	1	1.06	1.03	1.09	1.28	1.28	1.13	1.11
1	0	75.8	1.14	1.18	0	1	0	0	0	0	1	0	0	0	0	1	0	0.95	0.89	0.89	1.12	1.12	1.01	1.02
1	0	77.3	1.62	1.93	0	0	0	1	0	0	1	1	1	1	1	0	2	1.5	1.33	1.41	1.71	1.71	1.72	1.81
1	1	64.5	1.04	1.16	1	0	0	0	0	0	0	0	0	0	0	1	0	1.12	1.08	1.06	1.31	1.44	1.15	1.16
0	0	78	1.07	1.11	0	1	0	0	0	0	0	0	0	0	0	1	0	0.94	0.84	0.85	0.97	0.97	0.96	1.01
1	0	75.2	1.35	1.26	0	1	0	0	0	0	0	0	0	0	0	1	0	1.07	1.08	1.03	1.15	1.11	1.23	1.21

(Continued)

(Continued).

Sex	APOE	Age	ent_l	ent_r	K1	K2	K3	K4	K5	K6	K7	K8	K38	pk358	k358	k126	k348	abeta	medfront_L	medfront_R	postcng_L	postcng_R	precum_L	precum_R
1	1	71.1	1.33	1.28	1	1	0	0	0	0	0	0	0	0	0	2	0	1.6	1.71	1.71	1.74	1.8	1.73	1.77
1	0	76.7	1.15	1.11	0	1	0	0	0	0	0	0	0	0	0	1	0	1.24	1.39	1.36	1.29	1.22	1.2	
1	0	71.9	1.09	1.1	1	0	0	0	0	0	0	0	0	0	0	1	0	1.01	0.98	1.2	1.13	1.07	1.05	
0	0	80.7	1.63	1.72	0	0	0	0	0	0	1	1	1	1	1	0	1	1.49	1.41	1.63	1.67	1.7	1.7	
0	1	72.3	0.99	0.92	1	0	0	0	0	0	1	0	0	0	0	1	0	1.1	1.03	1.15	1.16	1.11	1.13	

```

library(car)
library(ggplot2)
library(Hmisc)
##### read
data #####
#####
dat = read.csv('C:...../subject_data.csv',
stringsAsFactors = FALSE)
dat1n = na.omit(dat)
dat1n$k1 = as.factor(dat1n$k1)
dat1n$k2 = as.factor(dat1n$k2)
dat1n$k3 = as.factor(dat1n$k3)
dat1n$k4 = as.factor(dat1n$k4)
dat1n$k5 = as.factor(dat1n$k5)
dat1n$k6 = as.factor(dat1n$k6)
dat1n$k7 = as.factor(dat1n$k7)
dat1n$k8 = as.factor(dat1n$k8)
dat1n$sex = as.factor(dat1n$sex)
dat1n$APOE = as.factor(dat1n$APOE)
##### backward
elimination #####
#
fit1 = lm(ent_L ~ k1 + k2 + k3 + k4 + k5 + k6 + k7 +
k8, data = dat1n)
selection = step(fit1, direction = "backward")
result_out = selection$coefficients
ouput_temp = summary(eval(selection$call))
adj_rsq = round(ouput_temp$adj.r.squared, 5)
##### second step: linear regres-
sion (determine positive and negative coeff) #####
####
fit2 = lm(ent_L ~ Age + sex + APOE + k1 + k2 + k3 +
k5 + k6 + k8, data = dat1n)
summary(fit2)
##### third step: linear regression
for composite scores #####
fit3 = lm(ent_L ~ Age + sex + APOE + k358 +k126,
data = dat1n)
summary(fit3)

```

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